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More than smell – COVID-19 is associated with severe impairment of smell, taste, and chemesthesis

By-line Authors:

Valentina Parma^{1*}, Kathrin Ohla^{2*}, Maria G. Veldhuizen^{3*}, Masha Y Niv⁴, Christine E Kelly⁵, Alyssa J. Bakke⁶, Keiland W. Cooper⁷, Cédric Bouysset⁸, Nicola Pirastu⁹, Michele Dibattista¹⁰, Rishemjit Kaur¹¹, Marco Tullio Liuzza¹², Marta Y. Pepino¹³, Veronika Schöpf¹⁴, Veronica Pereda-Loth¹⁵, Shannon B Olsson¹⁶, Richard C Gerkin¹⁷, Paloma Rohlf's Domínguez¹⁸, Javier Albayay¹⁹, Michael C. Farruggia²⁰, Surabhi Bhutani²¹, Alexander W. Fjaeldstad²², Ritesh Kumar²³, Anna Menini²⁴, Moustafa Bensafi²⁵, Mari Sandell²⁶, Iordanis Konstantinidis²⁷, Antonella Di Pizio²⁸, Federica Genovese²⁹, Lina Öztürk³⁰, Thierry Thomas-Danguin³¹, Johannes Frasnelli³², Sanne Boesveldt³³, Özlem Saatci³⁴, Luis R. Saraiva³⁵, Cailu Lin²⁹, Jérôme Golebiowski³⁶, Liang-Dar Hwang³⁷, Mehmet Hakan Ozdener²⁹, Maria Dolors Guàrdia³⁸, Christophe Laudamiel³⁹, Marina Ritchie⁴⁰, Jan Havlíček⁴¹, Denis Pierron⁴², Eugeni Roura⁴³, Marta Navarro⁴³, Alissa A. Nolden⁴⁴, Juyun Lim⁴⁵, KL Whitcroft⁴⁶, Lauren R Colquitt²⁹, Camille Ferdenzi⁴⁷, Evelyn V Brindha⁴⁸, Aytug Altundag⁴⁹, Alberto Macchi⁵⁰, Alexia Nunez-Parra⁵¹, Zara M. Patel⁵², Sébastien Fiorucci³⁶, Carl M Philpott⁵³, Barry C. Smith⁵⁴, Johan N. Lundström⁵⁵, Carla Mucignat⁵⁶, Jane K. Parker⁵⁷, Mirjam van den Brink⁵⁸, Michael Schmuker⁵⁹, Florian Ph.S Fischmeister⁶⁰, Thomas Heinbockel⁶¹, Vonnie D.C. Shields⁶², Farhoud Faraji⁶³, Enrique Santamaría⁶⁴, William E.A. Fredborg⁶⁵, Gabriella Morini⁶⁶, Jonas K. Olofsson⁶⁵, Maryam Jaleesi⁶⁷, Noam Karni⁶⁸, Anna D'Errico⁶⁹, Rafieh Alizadeh⁷⁰, Robert Pellegrino⁷¹, Pablo Meyer⁷², Caroline Huart⁷³, Ben Chen⁷⁴, Graciela M. Soler⁷⁵, Mohammed K. Alwashahi⁷⁶, Antje Welge-Lüssen⁷⁸, Jessica Freiherr⁷⁹, Jasper H. B. de Groot⁸¹, Hadar Klein⁴, Masako Okamoto⁸⁴, Preet Bano Singh⁸⁶, Julien W. Hsieh¹⁰⁸, GCCR Group Author, Danielle R Reed²⁹, Thomas Hummel¹⁰⁹, Steven D. Munger^{106, 110}, John E. Hayes⁶

Non by-line authors (to be listed as collaborators in PubMed under the GCCR Group Author):

Olagunju Abdulrahman⁷⁷, Pamela Dalton²⁹, Carol H. Yan⁸⁰, Vera V. Voznessenskaya⁸², Jingguo Chen⁸³, Elizabeth A. Sell⁸⁵, Julie Walsh-Messinger⁸⁷, Nicholas S. Archer⁸⁸, Sachiko Koyama⁸⁹, Vincent Deary⁹⁰, S. Craig Roberts⁹¹, Hüseyin Yanik⁹², Samet Albayrak⁹³, Lenka Martinec Nováková⁹⁴, Ilja Croijmans⁹⁵, Patricia Portillo Mazal⁹⁶, Shima T. Moein⁹⁷, Eitan Margulis⁴, Coralie Mignot⁹⁸, Sajidxa Mariño⁹⁹, Dejan Georgiev¹⁰⁰, Pavan K. Kaushik¹⁰¹, Bettina Malnic¹⁰², Hong Wang²⁹, Shima Seyed-Allaei⁹⁷, Nur Yoluk¹⁰³, Sara Razzaghi-Asl¹⁰⁴, Jeb M. Justice^{105, 106}, Diego Restrepo¹⁰⁷

¹Department of Psychology, Temple University, ²Institute of Neuroscience and Medicine (INM-3), Research Center Jülich, ³Department of Anatomy, School of Medicine, Mersin University, ⁴Institute of Biochemistry, Food Science and Nutrition, The Hebrew University of Jerusalem, ⁵AbScent, ⁶Department of Food Science, The Pennsylvania State University, ⁷Interdepartmental Neuroscience Program, University of California Irvine, ⁸Institut de Chimie de Nice, Université Côte d'Azur, ⁹Centre for Global Health Research, Usher Institute, The University of Edinburgh, ¹⁰Department of Basic Medical Sciences, Neuroscience and Sensory Organs, Università degli Studi di Bari A. Moro, ¹¹V1-B, CSIR-Central Scientific Instruments Organisation, ¹²Department of Medical and Surgical Sciences, "Magna Graecia" University of Catanzaro, ¹³Food Science and Human Nutrition, University of Illinois at Urbana Champaign, ¹⁴Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, ¹⁵GSBMS - Medecine

Evolutive UMR5288, Université de Toulouse, ¹⁶National Centre for Biological Sciences, National Centre for Biological Sciences, Tata Institute of Fundamental Research, ¹⁷School of Life Sciences, Arizona State University, ¹⁸Department of Psychology and Anthropology, University of Extremadura, ¹⁹Department of General Psychology, University of Padova, ²⁰Psychiatry, Yale University School of Medicine, ²¹Exercise and Nutritional Sciences, San Diego State University, ²²Department of Otolaryngology, Hospital Unit West, Aarhus University, ²³Biocomputation Group, University of Hertfordshire, ²⁴Neuroscience Area, SISSA, International School for Advanced Studies, ²⁵Neuropop Team, Lyon Neuroscience Research Center, CNRS UMR5292 - INSERM U1028 - University Lyon 1, ²⁶Department of Food and Nutrition, Functional Foods Forum, University of Helsinki, University of Turku, ²⁷Academic ORL Department, Aristotle University, ²⁸Section In-silico Biology and Machine Learning, Leibniz-Institute for Food Systems Biology at the Technical University of Munich, ²⁹Monell Chemical Senses Center, ³⁰Mersin University, ³¹CSGA-Centre for Taste and Feeding Behavior, INRAE, ³²Anatomy, Université du Québec à Trois-Rivières, ³³Division of Human Nutrition and Health, Wageningen University, ³⁴Otorhinolaryngology, Medical Science University, ³⁵Translational Medicine Division, Sidra Medicine, ³⁶Institut de Chimie de Nice, UMR CNRS 7272, Université Côte d'Azur, ³⁷The University of Queensland Diamantina Institute, The University of Queensland, ³⁸Food Technology, IRTA, ³⁹DreamAir Llc, ⁴⁰Neurobiology and Behavior, University of California, Irvine, ⁴¹Department of Zoology, Charles University, ⁴²Médecine Evolutive UMR5288, Université de Toulouse-CNRS, ⁴³Centre for Nutrition and Food Sciences, The University of Queensland, ⁴⁴Department of Food Science, University of Massachusetts, ⁴⁵Food Science and Technology, Oregon State University, ⁴⁶Ear Institute, UCL, ⁴⁷Lyon Neuroscience Research Center, Lyon Neuroscience Research Center, CNRS UMR5292 - INSERM U1028 - University Lyon 1, ⁴⁸EEE, Karunya University, ⁴⁹Otorhinolaryngology Department, Biruni University, ⁵⁰ENT Department, Italian Academy Of Rhinology - Assi Sette Llaghi Varese, ⁵¹Department of Biology, Universidad de Chile, ⁵²Otolaryngology - Head and Neck Surgery, Stanford University School of Medicine, ⁵³The Norfolk Smell & Taste Clinic, University of East Anglia, ⁵⁴Institute of Philosophy, University of London, ⁵⁵Department of Clinical Neuroscience, Karolinska Institutet, ⁵⁶Department of Molecular Medicine, University of Padova, ⁵⁷Department of Food and Nutritional Sciences, University of Reading, ⁵⁸Laboratory of Behavioural Gastronomy, Maastricht University, ⁵⁹Department of Computer Science, University of Hertfordshire, ⁶⁰Institute of Psychology, University of Graz, ⁶¹Department of Anatomy, Howard University College of Medicine, ⁶²Biological Sciences Department, Fisher College of Science and Mathematics, Towson University, ⁶³Otolaryngology-Head and Neck Surgery, University of California San Diego Health, ⁶⁴Clinical Neuroproteomics Unit, Navarrabiomed-IDISNA, ⁶⁵Department of Psychology, Stockholm University, ⁶⁶University of Gastronomic Sciences, ⁶⁷Skull Base Research Center, The Five Senses Institute, Iran University of Medical Sciences, ⁶⁸Internal Medicine Department, Hadassah Medical Center, ⁶⁹Neurobiology, Goethe Universität Frankfurt, ⁷⁰ENT and Head and Neck Research Center and Department, Hazrat Rasoul Hospital, the Five Senses Institute, Iran University of Medical Sciences, ⁷¹Food Science Department, University of Tennessee, ⁷²Health Care and Life Sciences, IBM T.J. Watson Research Center, ⁷³Otorhinolaryngology, Cliniques Universitaires Saint-Luc, Brussels University, ⁷⁴Psychiatry, Guangzhou Medical University, ⁷⁵Otorhinolaryngology, Buenos Aires University and GEOG (Grupo de Estudio de Olfato y Gusto), ⁷⁶Surgery Department, ENT Division, Sultan Qaboos University, ⁷⁷Department of Physiology, The Federal University of Technology, Akure, Nigeria, ⁷⁸Department of Otorhinolaryngology, University Hospital Basel, Basel, ⁷⁹Department of Psychiatry and Psychotherapy, FAU Erlangen, ⁸⁰Department of Surgery, Division of Otolaryngology, University of California San Diego, ⁸¹Psychology, Utrecht University, ⁸²Innovative Technologies, Severtsov Institute of Ecology and Evolution RAS, ⁸³Department of Otolaryngology-Head and Neck

Surgery, Second Affiliated Hospital of Xi'an Jiaotong University, ⁸⁴Department of Applied Biological Chemistry, The University of Tokyo, ⁸⁵Perelman School of Medicine, University of Pennsylvania, ⁸⁶Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, University of Oslo, ⁸⁷Psychology, University of Dayton, ⁸⁸Agriculture and Food, The Commonwealth Scientific and Industrial Research Organisation (CSIRO), ⁸⁹Department of Biology, Indiana University, ⁹⁰Department of Psychology, Northumbria University Newcastle, ⁹¹Division of Psychology, University of Stirling, ⁹²Electrical and Electronics Engineering, Mersin University, ⁹³Cognitive Science, Middle East Technical University, ⁹⁴Department of Anthropology, Charles University, Faculty of Humanities, ⁹⁵Faculty of Social and Behavioral Sciences, Utrecht University, ⁹⁶Servicio Otorrinolaringología, Hospital Italiano de Buenos Aires, ⁹⁷School of Biological Sciences, Institute for Research in Fundamental Sciences, ⁹⁸Department of Otorhinolaryngology, Smell and Taste Center, Dresden, ⁹⁹Founder and CEO, Centro de Otorrinolaringología Respira Libre, ¹⁰⁰Department of Neurology, University Medical Centre Ljubljana, ¹⁰¹National Center for Biological Sciences, Tata Institute of Fundamental Research, ¹⁰²Department of Biochemistry, University of São Paulo, Brazil, ¹⁰³Institute of Health Sciences, Mersin University, ¹⁰⁴Bilkent Brain Research Center, Bilkent University, ¹⁰⁵Department of Otolaryngology, ¹⁰⁶Center for Smell and Taste, University of Florida, ¹⁰⁷Department of Cell and Developmental Biology, University of Colorado Anschutz Medical Campus, ¹⁰⁸Rhinology-Olfactology Unit, ENT Department, Geneva University Hospitals, ¹⁰⁹Department of Otorhinolaryngology, TU Dresden, ¹¹⁰Department of Pharmacology and Therapeutics, University of Florida

Author note

Correspondence concerning this article should be addressed to:

Dr. John E. Hayes
 Department of Food Science
 Pennsylvania State University
 220 Erickson Food Science Building
 University Park, PA 16802 USA
 Email: jeh40@psu.edu
 Twitter: @TasteProf

Abstract

Recent anecdotal and scientific reports have provided evidence of a link between COVID-19 and chemosensory impairments such as anosmia. However, these reports have downplayed or failed to distinguish potential effects on taste, ignored chemesthesis, and generally lacked quantitative measurements. Here, we report the development, implementation and initial results of a multi-lingual, international questionnaire to assess self-reported quantity and quality of perception in three distinct chemosensory modalities (smell, taste, and chemesthesis) before and during COVID-19. In the first 11 days after questionnaire launch, 4039 participants (2913 women, 1118 men, 8 other, ages 19-79) reported a COVID-19 diagnosis either via laboratory tests or clinical assessment. Importantly, smell, taste and chemesthetic function were each significantly reduced compared to their status before the disease. Difference scores (maximum possible change ± 100) revealed a mean reduction of smell (-79.7 ± 28.7 , mean \pm SD), taste (-69.0 ± 32.6), and chemesthetic (-37.3 ± 36.2) function during COVID-19. Qualitative changes in olfactory ability (parosmia and phantosmia) were relatively rare and correlated with smell loss. Importantly, perceived nasal obstruction did not account for smell loss. Furthermore, chemosensory impairments were similar between participants in the laboratory test and clinical assessment groups. These results show that COVID-19-associated chemosensory impairment is not limited to smell, but also affects taste and chemesthesis. The multimodal impact of COVID-19 and lack of perceived nasal obstruction suggest that SARS-CoV-2 infection may disrupt sensory-neural mechanisms.

Introduction

In late 2019, a new virus, SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus strain 2), was reported in Wuhan, China (Zhu et al., 2020). The resulting COVID-19 disease has become a global pandemic with 3.18 million reported cases as of May 1, 2020 (World Health Organization, 2020). When assessing SARS-CoV-2 infection, clinicians initially focused on symptoms such as fever, body aches, and dry cough. However, emerging reports suggest sudden olfactory loss (anosmia or hyposmia) may be prevalent in patients with COVID-19 (Menni et al., 2020; Vetter et al., 2020). Olfactory disorders have long been associated with viral upper respiratory tract infections (URI) that cause the common cold and flu, including influenza and parainfluenza viruses, rhinoviruses, and other endemic coronaviruses (Soler et al., 2020). Taste disorders have been known to occur during and after respiratory viral infection, as well (Hummel et al., 2011). One case report found anosmia presenting with SARS (Hwang, 2006). Olfactory dysfunction due to viral infections may account for 11-45% of all olfactory disorders excluding presbyosmia (Nordin and Brömerson, 2008). The estimated prevalence of COVID-19-associated olfactory impairment may be higher than in COVID-19-independent postviral olfactory loss; estimations range from 5% to 85% in self-report studies, with differences noted between mild and severe cases (Bagheri et al., 2020; Gane et al., 2020; Giacomelli et al., 2020; Haldrup et al., 2020; Hopkins et al., 2020; Lechien et al., 2020a; 2020b; Mao et al., 2020; Menni et al., 2020; Yan et al., 2020a; 2020b). When psychophysical odor identification tests are used, this prevalence ranges from 76% in Europe using the Sniffin' Sticks (Lechien et al., 2020b)

to 98% in Iran using the UPSIT (Moein et al., 2020), though the severity of COVID-19 in these study cohorts may not be representative of the larger population. These anecdotes, pre-prints, letters, and peer-reviewed reports (for a review see, Pellegrino et al., in press), describe chemosensory disturbances in COVID-19 with characteristics that are similar to those seen in common URIs, such as isolated sudden onset of anosmia (Gane et al., 2020), occurrence of anosmia in mild or asymptomatic cases of COVID-19 (Hopkins et al., 2020), and loss of taste (Lechien et al., 2020a; Yan et al., 2020a). As of May 13, 2020, the European Centre for Disease Prevention and Control, the World Health Organization and the following countries or regions have listed smell loss as a symptom of COVID-19: Argentina, Chile, Denmark, Finland, France, Italy, Luxembourg, New Zealand, Singapore, South Africa, Slovenia, Spain, Switzerland, The Netherlands, and the United States of America (U.S.A.); many other countries or regions have not yet officially acknowledged smell loss as a symptom of COVID-19. To date, quantitative studies to determine the extent and detail of broad chemosensory changes in COVID-19 are rare, with the exception of two recent studies: Iravani et al. (2020), assessed odor intensity in a group of Swedish respondents, while Moein et al. (2020) tested a small sample of hospitalized Iranian patients with the University of Pennsylvania Smell Identification Test. We use three separate sensory modalities – smell, taste and chemesthesis – to sense our chemical environment in daily life. The olfactory system (smell) detects volatile chemicals through olfactory sensory neurons in the nasal cavity. Odors in the external environment are sampled through the nostrils (orthonasal olfaction), while odors coming from food or drink in the mouth are sampled via the nasopharynx (retronasal olfaction). The gustatory system (taste) responds to non-

volatile compounds in the mouth that elicit sensations of sweet, salty, bitter, sour and umami (savory). Finally, chemesthesis detects other chemicals, often found in herbs or spices, that evoke sensations like burning, cooling or tingling.

While taste has occasionally been explored with respect to COVID-19 (e.g., Giacomelli et al., 2020; Yan et al., 2020), chemesthesis remains unexamined in recent studies, despite anecdotal reports that it may be similarly compromised in persons with COVID-19. Smell, taste, and chemesthesis are often conflated, mostly because they produce a single experience of flavor during eating (Rozin, 1982; Spence et al., 2014; Duffy and Hayes, 2019; Hayes, 2019), and patients often report a loss of taste when in fact they are experiencing a loss of retronasal olfaction. Nevertheless, the olfactory and gustatory systems, along with parts of the somatosensory system that conveys chemesthesis, are separate sensory systems with distinct peripheral and central neural mechanisms (Shepherd, 2006; Green, 2012). To date, the impact of COVID-19 on each of these three chemosensory modalities remains poorly understood.

Chemosensory disturbances can result in quantitative reductions in smell or taste (i.e., anosmia/hyposmia and ageusia/hypogeusia, respectively), or as qualitative changes (e.g., distortions of smell and taste, termed parosmia and dysgeusia, or phantom sensations, termed phantosmia and phantogeusia). These key distinctions have been neglected in previous reports. Because these phenomena are not necessarily correlated and have different mechanisms (Holbrook et al., 2005; Iannilli et al., 2019; Reden et al., 2007), understanding how COVID-19 impacts chemosensation in

both quantitative and qualitative ways should provide important insights into the mechanisms by which the SARS-CoV-2 virus affects the chemical senses.

Ideally, validated testing of chemosensory function would be combined with a review of a patient's medical records, including laboratory test results (from viral swab or serology, "Lab Test") to confirm the infectious agent. Due to limited laboratory test availability in many countries, the necessity in some medical settings for social distancing, and a potentially large number of asymptomatic or mild cases, it has been impractical or impossible to conduct such chemosensory testing for many individuals with COVID-19. Additionally, in many countries where testing resources are limited, laboratory testing has been limited to the most severe cases. Another diagnosis method is a clinical assessment by a medical professional ("Clinical Assessment"), either in-office or remotely via tele-medicine. Thus, the method of diagnosis – Lab Test versus Clinical Assessment – may be associated with differences in symptom severity, including severity of chemosensory impairments. To account for possible differences in the severity of infection as well as the availability of diagnosis options across countries, we collected information on diagnosis methods and compared chemosensory function between participants diagnosed with Lab Test vs. Clinical Assessment.

Given all the issues raised above, we deployed a crowd-sourced, multilingual, online study with a global reach (as of May 1, 2020 deployed in 27 languages); this survey has the potential to provide reproducible data from a large number of participants around the world. In this pre-registered report, we present data from 4039 participants who reported a COVID-19 diagnosis either via Lab Test or Clinical Assessment and who

completed the questionnaire during the first 11 days the study was available online. Here we address two main research questions. First, we asked what chemosensory changes are observed in participants with COVID-19, compared to before illness (i.e., within participants). Next, we asked whether the two diagnostic groups differ in chemosensory changes (i.e., between participants). For both diagnosis methods, we observed significant quantitative changes in smell, taste, and chemesthesis with COVID-19. Most chemosensory loss could not be accounted for by self-reported nasal obstruction, a factor commonly associated with diminished smell in other upper respiratory diseases (Doty, 2001). Further, we found little incidence of qualitative changes in olfactory function, with only a small percentage of participants reporting distorted smells (consistent with parosmia) or phantom smells (consistent with phantosmia). Together, these results provide an initial assessment of comprehensive chemosensory impairments associated with COVID-19.

Methods

Preregistration

We preregistered our hypotheses and analyses on April 19, 2020, at 12:20 AM Eastern Daylight Time (EDT), before the data became available (data reflected questionnaires submitted between April 7, 2020 6:00AM EDT and April 18, 2020 at 8:34 AM EDT) (Veldhuizen et al., 2020). In line with the pre-registration, and according to the Sequential Bayes Factor Design (*section 2.3*), one of the authors (AJB) not involved in the development of the pre-registration queried the database to check whether the

minimum number of participants per group was reached. The data reported in this manuscript, along with analysis scripts, will be available at OSF (<https://osf.io/a3vkw/>) upon the acceptance of the manuscript. The project is structured according to the research compendium created with the *rrtools* package (Marwick, 2019). The presented analyses are as pre-registered, unless specified otherwise.

The GCCR core questionnaire

The GCCR questionnaire [Supplementary Materials, and included in the list of research tools to assess COVID-19 by the NIH Office of Behavioral and Social Sciences Research (OBSSR, Anonymous, 2020)], measures self-reported smell, taste, and chemesthesis function as well as nasal blockage in participants with respiratory illness, including COVID-19, within the two weeks prior to completing the questionnaire. It was created iteratively through a crowdsourced approach with a preliminary period of development and commentary across an international group of chemosensory experts, clinicians and patients advocates. Relevant to the scope of the present manuscript, participants were asked to quantify their ability to smell, taste, and perceive cooling, tingling and burning sensations (chemesthesis) before and during the COVID-19, on separate, horizontally-presented, 100-point visual analogue scales (VAS). Participants were also asked to quantify their perceived nasal obstruction on a 100-point VAS with “not at all blocked” and “completely blocked” as anchors. Framing the questions in terms of ability, rather than intensity, was driven by the desire to be readily understood by participants without additional training or instructions and was informed by spontaneous patient reports, internet search trends and in dialogue with patient advocates (e.g., we

implicitly separated taste / chemesthesis experienced in the mouth from orthonasal smell as experienced in the nose, in full alignment with the ecological framework first proposed by Gibson in 1966. Specifically, for taste, we stated “The following questions are related to your sense of taste. For example, sweetness, sourness, saltiness, bitterness experienced in the mouth.” For chemesthesis, we stated “The following questions are related to other sensations in your mouth, like burning, cooling, or tingling. For example, chili peppers, mint gum or candy, or carbonation. In both cases, we were orienting participants toward sensations that are experienced in the mouth. In contrast, for smell, we stated “These questions relate to your sense of smell (for example, sniffing flowers or soap, or smelling garbage) but not the flavor of food in your mouth.” The within-subject nature of the present design precludes a need for more sophisticated scaling methods than a VAS (Kalva et al., 2014). That is, participants were not randomly assigned to the two diagnostic groups; however, the groups may be considered as if random when it comes to adjective interpretation / scale usage. This case, we argue, would fall within Bartoshuk’s guidelines for when valid across group comparisons can be made with a VAS (Bartoshuk et al., 2003). For a list of the questions analyzed in the present work, please see Figure S2.

Participants were also asked to report demographic information (i.e., year of birth, gender, and country of residence) as well as information related to their COVID-19 diagnosis and their respiratory illness-related symptoms, including smell and taste, in check-all-that-apply (CATA) format. We summarized the questions used in the present study in Supplementary Figure S1. Please refer to the full questionnaire, included in the

Supplementary materials, for question order and the labels on the anchors of each question.

The questionnaire was implemented in 10 languages as of April 18th, 2020 (the date on which the database was last queried for this report): English, French, German, Italian, Japanese, Kannada, Norwegian, Spanish, Swedish, and Turkish. Our translation protocol was modeled after the process developed by the Psychological Science Accelerator (Moshontz et al., 2018). Briefly, translations of the original English questionnaire involved three steps: i) the original (English) questionnaire was translated to the target language by independent translators, resulting in Translation Version A; ii) Version A was translated back from the target language to English by a separate group of independent translators, resulting in Version B; iii) Versions A and B were discussed among all translators, with the goal of resolving potential discrepancies between the two versions, resulting in the final Version C. All questionnaires in all languages were then implemented in Compusense Cloud, Academic Consortium (Guelph, Ontario), a secure cloud-based data collection platform with multilingual support. Please refer to the supplementary materials for the full survey (Supplementary Materials) and to the questions from the survey analyzed in the present work (Figure S1).

Study design

This study compares self-reported quantitative changes (during vs. before the illness) in smell, taste, chemesthesis, and nasal obstruction as well as qualitative changes in smell and taste between two groups of respondents: those who reported a COVID-19 diagnosis as a result of an objective test such as a swab test ("Lab Test") or

those who reported a diagnosis from clinical observations by a medical professional (“Clinical Assessment”). Given the lack of effect size estimates in the literature, we employed a Sequential Bayes Factor Design (SBFD) that allows optional stopping with unlimited multiple testing (Schönbrodt et al., 2017). Specifically, we used a SBFD with a minimal number of participants and a temporal stopping rule to increase the probability of obtaining the desired level of evidence and to reduce the probability of obtaining misleading evidence. The desired grade of relative evidence for the alternative vs. the null (BF_{10}) hypothesis is set at $BF_{10} > 10$ (strong evidence) for H_1 and $BF_{01} > 6$ (moderate evidence) for H_0 . We derived the minimal $N_{\min} = 480$ per group to start SBFD through a Bayes Factor Design Analysis (BFDA) for fixed-n designs (Schönbrodt and Wagenmakers, 2018) for a two-independent-sample, two-sided testing, and a conservative Cohen’s $D = 0.2$ with 80% power of reaching a $BF_{10} > 10$ and a $BF_{01} > 6$ with a default prior. Our stopping rule follows a temporal criterion (data collection until April 18, 2020, 8:34 AM EDT) and N_{\min} . BF computation continues with every 20 participants added in the slowest accumulating group at a time until the thresholds of H_1 or H_0 are reached.

Study setting

Participation in this online study was voluntary and participants received no remuneration. Inclusion criteria were: consent to participate, age 19 years and older (based on birth year), and any form or suspicion of respiratory illness in the past two weeks. Participants were asked about their year of birth and the onset of their illness during the survey to confirm the inclusion criteria, and the survey terminated for non-

eligible participants via branching logic. The nature of the questionnaire necessitated at least some secondary education in terms of language and distribution method (web survey) as well as internet access. The protocol complies with the revised Declaration of Helsinki and was approved as an exempt study by the Office of Research Protections at The Pennsylvania State University (Penn State) in the U.S.A. (STUDY00014904). The questionnaire was distributed globally in the different languages through traditional (i.e., print, television, radio) and social media (e.g., Twitter, Facebook), the website of the Global Consortium for Chemosensory Research (GCCR; <https://gcchemosensr.org>), flyers, professional networks, and word of mouth. All data were collected from a non-representative, convenience sample via Compusense Cloud, which is compatible with use on a smartphone, tablet, laptop, or desktop computer. Data collection was compliant with privacy laws in the U.S.A. and the European Union [including California and General Data Protection regulation (GDPR) rules].

Participants

At the close of data collection on April 18, 2020, 4039 participants with a diagnosis of COVID-19 completed the ratings for smell, taste, chemesthesis ability, and nasal obstruction before and during their recent illness and were included in the present study. Participants who did not complete all ratings as mentioned above and/or gave inconsistent responses in three questions that addressed changes in smell perception (specifically, selecting changes in smell in “Have you had any of the following symptoms with your recent respiratory illness or diagnosis?”, reporting a difference of at least 5 points in “Rate your ability to smell before your recent respiratory illness or diagnosis”

and/or select at least one answer at the question “Have you experienced any of the following changes in smell with your recent respiratory illness diagnosis?”) or reported an age above 100 ($n = 1$) were excluded from the sample. Of those included in the final sample, 2913 were women, 1118 were men, 3 were other and 5 preferred not to say. Overall the age of the participants ranged from 19 to 79 years old (mean \pm sd: 41.38 ± 12.20 years old).

Here, we will compare respondents from two diagnostic groups: (a) participants who reported that their COVID-19 diagnosis was confirmed via objective Lab Test ($N = 1402$: 1064 F, 335 M; age mean \pm sd: 40.73 ± 12.29 years old) compared with (b) participants who reported that their COVID-19 diagnosis was obtained via clinical observation by a medical professional ($N = 2637$: 1849 F, 783 M; age mean \pm sd: 41.72 ± 12.14 years old). Based on self-report, respondents indicated they resided in the following countries: Algeria, Argentina, Australia, Austria, Belgium, Brazil, Canada, Colombia, Costa Rica, Czech Republic, Denmark, Ecuador, Egypt, France, Germany, Greece, Iran, Ireland, Italy, Luxembourg, Morocco, Mexico, Netherlands, New Zealand, Norway, Paraguay, Portugal, Romania, Russia, Singapore, Slovenia, South Africa, Spain, Sweden, Switzerland, Thailand, Tunisia, Turkey, UK, United Arab Emirates, U.S.A. Figure 1 illustrates the derivation of the sample presented here.

*** Figure 1 here ***

Statistical analysis

All analyses were performed in R (Team R Core Development, 2013) via RStudio. The scripts along with information on the computational environment and dependencies

will be found, upon acceptance of the manuscript, at <https://osf.io/a3vkw/>. Information on the computational environment and dependencies used is also shared for future reproducibility. The code will be also available on GitHub at <https://github.com/GCCR/GCCR001>, and will include a Jupyter notebook replicating the core analyses in Python.

We hypothesized there would be no difference between groups. Therefore, we elected for a Bayesian approach, which allows us to estimate the strength of evidence supporting the null hypothesis, over a frequentist approach that would only allow us to present evidence against the null hypothesis. To test our hypotheses (H_0 : no difference between groups; H_1 : difference between groups) in this between-participant SBFD, we conducted a Bayesian linear regression with the *lmBF* function from the *BayesFactor* package (Morey and Rouder, 2018) to detect changes (during minus before COVID-19) in smell, taste and chemesthetic abilities as well as nasal obstruction. Data report the Bayes factor and no proportional error estimate on the Bayes factor since they were all lower than $2.07e-05$. We used the default Cauchy prior on the effect sizes under the H_1 as the scale parameter spread which was set at its default value of $r = \sqrt{2}/2$. We performed robustness (sensitivity) checks by adjusting the Cauchy distribution to $r = 0.5$ and $r = 1$ to assess how the choice of prior affects the conclusions drawn from the analysis. We first assessed whether the model provides evidence in favor of H_1 or H_0 . To interpret the strength and the direction of those effects, we sampled from the models' posterior distributions (iterations = $1e4$). Please refer to the pre-registration and the analysis script (see above) for further details. As reported in Table 1, the interpretation of

the Bayes factors BF_{10} follows the classification scheme proposed by Lee and Wagenmakers (2013) and adjusted from (Jeffreys, 1961).

*** Table 1 here ***

Exploratory non-preregistered analyses

To quantify the association between the reports of (a) parosmia and phantosmia, (b) smell, (c) taste, (d) chemesthesis, and (e) a change in perceived nasal obstruction, we computed a correlation matrix that is visualized with *ggstatsplot* (Patil and Powell, 2018). To assess whether the proportion of parosmia and phantosmia reports differs between groups, we used a two-sample test for equality of proportions with a continuity correction. To characterize the relationship between perceived nasal blockage and chemosensory change, we used a principal component analysis (PCA) using *prcomp* from the R default *stats* package and we plotted the results with functions from the *FactoMineR* package (Lê et al., 2008). Additionally, to test whether different chemosensory function profiles exist in our sample, we performed a cluster analysis. The best clustering scheme was with 3 clusters as determined with *NbCluster* (Charrad et al., 2014), which tests 30 methods that vary the combinations of number of clusters and distance measures for the k-means clustering. Cluster stability was estimated through a bootstrapping approach (100 iterations) with the *bootcluster* package (Yu, 2017).

Results

Degree of smell loss during COVID-19

Overall, participants reported a large reduction in the sense of smell (-79.7 ± 28.7 points on the 100-point scale; mean \pm sd). Such decrease in the ability to smell was confirmed with extreme evidence (smell change against zero: $BF_{10} = 4366.29 \pm 0\%$) and that was similar for both groups ($BF_{10} = 2.17 \pm 0\%$ inconclusive evidence for a group difference, i.e. H_1 ; Figure 2A). The Clinical Assessment group exhibited a larger variance in the ability to smell during the illness as compared to the Lab Test group (Levene test, $F_{(1,4037)} = 6.81$, $p = 0.009$; see also the box plots in Figure 2A).

*** Table2 here ***

*** Figure 2 here ***

Smell qualitative changes

Parosmia did not differ significantly between groups ($X^2_{(1)} = 0.54$, $p = 0.463$ [-0.01 – 0.03]) and was reported by 7.77% (205 out of 2637) of participants in the Clinical Assessment and in 7.13% (100 out of 1402) the Lab Test group. Reports of phantosmia, however, did significantly differ between groups ($X^2_{(1)} = 13.8$, $p < 0.001$ [0.02 – 0.06]): it was reported by 9.44% (249 out of 2637) of participants in the Clinical Assessment and in 6.28% (88 out of 1402) the Lab Test group. Reports of either parosmia or phantosmia

negatively correlated with a report of a reduced ability to smell (on VAS) or a total smell loss (reported via CATA). Parosmia and phantosmia positively correlated with changes in smell, taste, and chemesthesis ratings but not with changes in perceived nasal obstruction (Figure 3).

*** Figure 3 here ***

Degree of taste loss in COVID-19

Similar to what was seen with smell loss, we observed an overall reduced ability to taste (-69.0 ± 32.6 points; mean \pm sd) that was confirmed with extreme evidence (taste change against zero: $BF_{10} = 3424.52 \pm 0\%$) and that was similar for both groups ($BF_{10} = 0.72 \pm 0\%$ suggesting inconclusive evidence for a group difference). The Clinical Assessment group exhibited a larger variance in the ability to taste during COVID-19 as compared to the Lab Test group (Levene test: $F_{(1,4037)} = 3.91$, $p = 0.048$; see also the box plots in Figure 2B).

Taste quality-specific changes

Participants were given the option to report changes in specific taste qualities (i.e., salty, sour, sweet, bitter or umami/savory) as a CATA question. Of all participants, 40% in both groups did not respond, 11% in both groups reported impairment of a single taste quality, and 48% reported impairment of two or more taste qualities (48% in the Clinical Assessment group, 49% in the Lab Test group). Between groups, only umami (savory) taste change was less frequently reported (25%) in the Clinical Assessment group than in the Lab Test group (29%; $X^2(1) = 7.22$, $p < 0.007$ [$-0.07 - -0.01$]). No significant

differences in the frequency of reporting changes for sweet, salty, bitter or sour taste was evident between groups (Table 3).

*** Table 3 here ***

Degree of chemesthesia loss in COVID-19

Similar to taste and smell, we observed an overall loss of chemesthetic ability (-37.3 ± 36.2 ; mean \pm sd) that was confirmed with extreme evidence (chemesthetic change against zero: $BF_{10} = 1459.98 \pm 0\%$) and that was similar for both groups ($BF_{01} = 35.42 \pm 0\%$ suggesting strong evidence against a group difference, Figure 2C). The distribution of chemesthetic ability showed a large 95%-CI $[-2.82 - 1.88]$.

Perceived nasal obstruction in COVID-19

We observed a disease-related change in perceived nasal obstruction that was supported by extreme evidence (nasal obstruction change against zero: $BF_{10} = 783.25 \pm 0\%$). No difference in the change in perceived nasal obstruction was found between groups as corroborated by moderate evidence against a group difference ($BF_{01} = 14.52 \pm 0\%$; Figure 4A).

To further characterize potential relationships between changes in perceived nasal obstruction and reports of changes in the three chemosensory modalities, we computed a Principal Component Analysis (Figure 4B). Changes in smell, taste, and chemesthesia ratings (during minus before) correlated strongly with component 1 (smell: $r = 0.72$; taste: $r = 0.84$; chemesthesia: $r = 0.74$), which explained 45.2% of the total multidimensional variance (inertia). By contrast, change in perceived nasal obstruction

was strongly anti-correlated ($r = -0.97$) with the orthogonal component 2, which explains 24.6% of the total inertia. These results indicate statistical independence of changes in chemosensory ability and perceived nasal obstruction. That is, changes in chemosensory ability and perceived nasal obstruction are statistically independent, so we conclude that changes in olfactory function in COVID-19 positive individuals cannot be attributed to nasal obstruction.

*** Figure 4 here ***

Chemosensory clustering

We used *k-means* algorithm to cluster respondents based on the similarities and differences in smell, taste, and chemesthesis change (Figure 5). Despite the changes being continuous in the three dimensions, a data-driven, 3-cluster solution (bootstrapped stability = 0.94) identified three groups. Based on the centroid positions, such groups can be described by degree of smell and taste loss and degree of chemesthesis loss. Cluster 1 (N = 1767, blue) groups participants whose ratings are centered around substantial smell, taste and chemesthesis loss (centroids: smell: -88.89, taste: -86.74, chemesthesis: -72.39). Cluster 2 (N = 1724, orange) groups participants whose ratings are centered around substantial smell and taste loss and rather unaffected chemesthesis (centroids: smell: -87.81, taste: -65.97, chemesthesis: -11.07). Cluster 3 (N = 548, green) groups participants whose ratings are centered around moderate smell and taste reduction and rather unaffected chemesthesis (centroids: smell: -24.33, taste: -20.97, chemesthesis: -6.87).

*** Figure 5 here ***

Discussion

Our study confirms and substantially extends previous reports showing that smell loss and taste loss are associated with COVID-19. Similar to other recent studies (Bagheri et al., 2020; Chen et al., 2020; Gane et al., 2020; Giacomelli et al., 2020; Haldrup et al., 2020; Hopkins et al., 2020; Lechien et al., 2020a, 2020b; Mao et al., 2020; Menni et al., 2020; Moein et al., 2020; Yan et al., 2020a, 2020b), we find that the majority of our participants with COVID-19 reports a severe reduction in the ability to smell as compared to before the onset of that disease. Notably, this smell loss was not associated with self-reported nasal obstruction, consistent with anecdotal reports. Further, we find that qualitative changes in smell (smell distortions or phantoms) were relatively rare. We found that taste, and to a lesser degree chemesthesis, were also significantly impaired for individuals with COVID-19. Together, these results suggest that COVID-19 broadly impacts chemosensory function across multiple sensory modalities, and that disruption of these may be a possible indicator of COVID-19.

This project is distinct from prior studies on the links between chemosensory dysfunction and COVID-19 in that it leverages a massive crowd-sourced, multinational approach to attack this urgent issue, and does so within a collaborative open science framework. This initial report is based on data in 10 languages from 41 countries; since the first tranche of data on April 18, 2020, 18 additional languages have been added on a rolling basis. The multinational, collaborative nature of the GCCR approach also sets it apart from other recently developed tools. Our hope is that an inclusive globally deployed assessment, coupled with publicly accessible data shared under contemporary

open science best practices, will serve as a foundation for future work. It is a limitation of this initial snapshot, however, that participants from different countries are not evenly represented. Cultural biases or country-specific manifestations of COVID-19 could potentially impact these results and will be explored by GCCR in future studies. Though our comprehensive self-report survey cannot replace in-person testing in a controlled clinical or laboratory setting, the gold standard for assessing alterations in chemosensory function, it efficiently and effectively addresses an emerging public health crisis with global scope of coverage. Thus, the model shown in this study of remote smell and taste assessment utilizing the internet may represent one way of reducing delays in assessment until aggressive physical distancing ends (Patel, 2020; Workman et al., 2020).

The mean change in ability to smell was substantial. Prior to onset of COVID-19, the mean rating for the ability to smell was over 90 on a 100-point VAS, yet during the disease, the mean rating dropped below 20. These data do not allow us to differentiate between individuals with partial (hyposmia) versus total loss (anosmia), and participants themselves may be unable to precisely characterize their degree of loss in the absence of objective olfactory testing (Hoffman et al., 2016; Loetsch and Hummel, 2019; Welge-Lüssen et al., 2005). Still, we can conservatively conclude that a major drop in the ability to smell is a hallmark of COVID-19. If the prevalence of COVID-19-associated smell loss is greater than that reported for the common cold or influenza (Beltrán-Corbellini et al., 2020), a different mechanism for disrupting olfactory function may be at play, or this

difference could also reflect increased tropism of SARS-CoV-2 for olfactory tissues (Baig et al., 2020).

Critically, the self-reported smell loss we observed is statistically independent of self-reported nasal obstruction. In common URIs, nasal obstruction can explain temporary smell impairments, a phenomenon many individuals have experienced in daily life. Here, estimates of nasal obstruction were based solely on self-report (we asked participants to rate the amount of “nasal blockage”); our data do not include objective, clinically validated measures of nasal breathing or obstruction. While nasal congestion does occur with COVID-19, it appears to be relatively rare in our sample. Still, the fact that many of our participants report substantial loss of olfactory function in the absence of concomitant nasal blockage seems remarkable.

In other instances of post-viral smell loss, about half of patients also experience a qualitative change in smell (Frasnelli et al., 2004; Reden et al., 2007; Rombaux et al., 2009). By contrast, less than 10% of participants in this study reported parosmia or phantosmia symptoms. The rarity of qualitative changes in smell may be a hallmark of COVID-19-associated smell impairments. Alternatively, the present study may not have fully captured qualitative changes in smell, as they tend to emerge later in the course of other disorders (Bonfils et al., 2005) and the present assessment was limited to within at most two weeks of suspected illness or diagnosis. Further studies are needed to more comprehensively address this issue.

While taste loss has also been associated with COVID-19 in patient anecdotes and a few studies, in most cases it has not been clearly differentiated from changes in smell.

Here, we found that ratings of taste function were, like those for smell, substantially decreased in individuals with COVID-19. Participant ratings for taste function dropped from a mean of ~ 91 before COVID-19 onset to less than ~24 during the disease. It is well established that people often confuse changes in retronasal olfaction – an important component of flavor perception during eating and drinking – with a true taste loss. While we cannot rule this out completely given the study design, ~60% of those reporting a taste loss also reported a decrease in their perception of at least one specific taste quality, with salty taste being the most common selection. The question on taste qualities is a CATA (check all that apply) question, which means that the subjects can choose any taste qualities that they believe were clearly affected. Indeed, many of the participants chose multiple taste qualities. These data support an interpretation that at least some participants were properly discerning taste from flavor. The observation that some participants reported loss of only a subset of taste qualities may reflect their difficulty in correctly identifying and naming individual taste qualities (Pilkova et al., 1991; Welge-Luessen et al., 2011) rather than quality-selective hypogeusia/ageusia (e.g., Gudziol and Hummel, 2007; Henkin et al., 1970; Lugaz et al., 2002; Huque et al., 2009). However, these possibilities cannot be clarified with the present database.

Compared to smell, the literature has described fewer examples of post-viral taste loss (Adour, 1994; Rubin and Daube, 1999). As the number of people responding to this questionnaire continues to grow on a rolling basis, the differences among different types of respiratory illnesses and their relationship to the degree of taste loss will be a major focus of forthcoming analyses.

Perhaps our most surprising finding was a notable loss of oral chemesthesis ability with COVID-19. Though the decrease is not as large as seen for smell and taste – an ~46% rating reduction for chemesthesis as compared to ~89% and ~76% percentage drop in smell and taste, respectively – it is significant. Interestingly, impairment of chemesthesis was typically accompanied by either taste and smell loss, while taste and smell loss could appear with normal chemesthesis. While nasal chemesthesis experienced with the inhalation of noxious chemicals like ammonia or ethanol is sometimes confused with smell, oral chemesthesis responses to compounds like capsaicin from chili peppers or menthol from mint rarely is (Green, 1996). Though predominantly thought of as the chemical activation of trigeminal afferents carrying temperature, pain or vibration information from the oral, nasal and eye mucosa, other somatosensory nerves, including in the mouth, can also be affected (Green, 1996; McDonald et al., 2016). Chemesthesis (and taste) has been reported to accompany post-viral hyposmia resulting from a URI, at least in some cases (Ren et al., 2012; de Haro-Licer et al., 2013; Pellegrino et al., 2017; Fark and Hummel, 2013). Together with our findings for smell and taste, these data suggest that SARS-CoV-2 impacts all three major chemosensory modalities. The mechanisms are not clear and may be distinct for each chemosensory system. For example, transcriptomic studies of the olfactory mucosa of mouse and human suggests that sustentacular, Bowman's gland, microvillous cells and stem cell populations, not olfactory sensory neurons themselves, contain ACE2, a receptor required for SARS-CoV-2 viral entry into cells. (Brann et al., 2020; Fodoulou et al., 2020). The pattern of ACE2 expression indicates SARS-CoV-2 may infect tongue keratinocytes (Venkatakrishnan et al., 2020) but it is not known if taste

receptor cells or cranial nerves carrying taste or chemesthetic information can be infected by SARS-CoV-2. This virus could alternatively infect surrounding epithelia or blood vessels (Sungnak et al., 2020; Varga et al., 2020), or perhaps even target cells of the central nervous system (Baig et al., 2020).

Based on the stark changes in ratings reported here, one may speculate that both smell and taste loss in COVID-19 are all-or-none phenomena. Although, we cannot rule out that this is an artifact of scale usage, this explanation seems unlikely, as the distribution of the chemesthetic ability ratings is roughly rectangular. This suggests that the all-or-none effect observed for smell cannot be simply attributed to participants using the scale in a discrete rather than continuous fashion. The self-reporting of olfactory function has been used in numerous studies; however, it is not unanimously accepted as it may suffer from low validity (Landis et al., 2003) due to under- and overreporting biases (Dalton and Hummel, 2000; Oleszkiewicz et al., 2020) and possible arbitrary usage. These studies all indicate that self-report ratings are far from being completely inaccurate, especially in participants with severe hyposmia or anosmia, with reported accuracy rates of 70-80% (Lötsch et al., 2019, Hoffman et al., 2016; Rawal et al., 2015).

Here, we account for well-known individual differences in baseline chemosensory abilities, as well as use of rating scales, by using a within-subject design where participants rate their abilities for different time points (before and during COVID-19). We perform an analysis of differences between two assessments (e.g. during minus before COVID-19) rather than on absolute ratings. To better address the question of validity of change in ability ratings, future studies should compare these self-reported and recalled

ratings to validated clinical tests before and during the individual's respiratory illness. However, in times of pandemic, the advantages of a remote assessment method may outweigh the potential decrease in validity compared to face-to-face clinical measures of taste and smell. Still, we acknowledge that a convenience sample recruited online may not be representative of the general population; thus, our study and others that use this type of recruitment approach (e.g., Menni et al., 2020; Iravani et al., 2020) should not be used to estimate prevalence of chemosensory loss in individuals with COVID-19.

Lastly, we found that mean impairments of smell, taste, and or chemesthesis did not differ between study participants who reported a COVID-19 diagnosis based on a Lab Test and those who reported diagnosis based on a Clinical Assessment. However, the Clinical Assessment group exhibited a larger variance in chemosensory loss than the Lab Test group. This could reflect more variability in the accuracy of the diagnosis, as the Clinical Assessment group may include individuals who were misdiagnosed and actually have another viral illness and/or a milder form of the disease. Determining whether the degree of change in chemosensory ability differs between COVID-19-positive individuals and those who are COVID-19-negative but have another respiratory disease will require specific comparisons between those two groups in a future study.

Conclusions

The GCCR consortium shows how health professionals, clinicians, patient advocates, and scientists can work together to undertake large-scale ground-breaking research of acute public health significance. The present research sets an example of how an emergent response to a global pandemic can be tackled with a crowd-sourced initiative that combines rigorous scientific standards with open-science practices. The established network, research infrastructure, protocol, and findings have the potential to influence current theories on the effects and mechanisms of COVID-19 on the chemical senses and to fuel future research in other areas.

Tables

Table 1. Interpretation of the Bayes factors BF_{10} follows the classification scheme proposed by Lee and Wagenmakers (2013) and adjusted from Jeffreys (1961).

Bayes Factor	Evidence Category
>100	Extreme evidence for H_1
30 - 100	Very strong evidence for H_1
10 - 30	Strong evidence for H_1
3 - 10	Moderate evidence for H_1
1 - 3	Anecdotal evidence for H_1
1	No evidence
$1/3 - 1$	Anecdotal evidence for H_0
$1/10 - 1/3$	Moderate evidence for H_0
$1/30 - 1/10$	Strong evidence for H_0
$1/100 - 1/30$	Very strong evidence for H_0
$< 1/100$	Extreme evidence for H_0

Table 2. Mean and standard deviation (SD) for the ratings of smell, taste, chemesthesis, and nasal obstruction before and during COVID-19 in the Clinical Assessment and Lab Test groups.

Variable	Clinical Assessment				Lab Test			
	Before COVID-19		During COVID-19		Before COVID-19		During COVID-19	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Smell	90.18	14.92	11.49	24.24	90.96	15.71	9.46	22.33
Taste	91.33	13.25	23.34	29.36	92.00	14.34	21.23	28.71
Chemesthesis	84.96	18.74	47.48	32.17	83.72	22.1	46.68	32.2
Nasal Obstruction	9.83	18.41	31.67	32.11	9.35	17.89	32.67	31.62

Table 3. Frequency of responses, by group, for changes of specific taste qualities during COVID-19.

Taste change	Clinical Assessment (N = 2637)	Lab Test (N=1402)
Sweet	1160	628
Salt	1211	629
Bitter	1036	550
Sour	980	531
Umami	668	411

Figure Legends

Figure 1. Flow diagram showing the selection of individual observations included in the reported analysis as well as the observations that were excluded.

Figure 2. Raincloud plots representing ratings for smell (A), taste (B), and chemesthesis (C) before (left) and during (right) COVID-19. Within each subplot (from left to right), ratings from single participants are displayed as dots. Boxplots show the 1st to 3rd quartiles, the horizontal line denotes the median, and whiskers denote 1.5 times the interquartile range. The density distribution of the data shows the proportions of given ratings. COVID-19 diagnosis is coded such that Clinical Assessment is a lighter shade and Lab Test is a darker shade.

Figure 3. Correlation matrices for individuals who reported parosmia (left, $n = 296$) and phantosmia (right, $n = 324$) across groups. The numbers refer to significant correlations at $p < 0.001$ (Adjustment: Holm).

Figure 4. Nasal obstruction. A) The raincloud plot represents ratings for perceived nasal obstruction. From left to right, ratings from single participants are displayed as dots. Boxplots show the 1st to 3rd quartiles, the horizontal line denotes the median, and whiskers denote 1.5 times the interquartile range. The density distribution of the data shows the proportions of given ratings. COVID-19 diagnosis is color-coded, with Clinical Assessment in lighter shade and Lab Test in darker shade. B) Principal component analysis. Correlation circle of the perceptual changes with the 1st (abscissa) and 2nd (ordinate) principal components (PCs).

Figure 5. A) Correlations between the three principal components with respect to changes in three chemosensory modalities (i.e. taste, smell, and chemesthesis). Shades of gray indicate positive correlation, whereas shades of red indicate negative correlations. White denotes no correlation. B) Clusters of participants identified by *k-means* clustering. The scatterplot shows each participant's loading on PC 1 (abscissa) and PC 2 (ordinate). Based on the centroid position, cluster 1 (blue, $N=1767$) groups participants who reported high degree of smell, taste and chemesthesis loss; cluster 2 (orange, $N=1724$) groups participants who reported high degree of smell and taste loss, and rather unaffected chemesthesis; cluster 3 (green, $N=548$) includes participants who reported moderately reduced smell and taste and rather unaffected chemesthesis.

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References

- Adour, K. K. (1994). Otological complications of herpes zoster. *Annals of Neurology*, 35(1 S), S62–S64. <https://doi.org/10.1002/ana.410350718>
- Anonymous. (2020). COVID-19 OBSSR research tools. Retrieved on May 1, 2020 from https://www.nlm.nih.gov/dr2/COVID-19_BSSR_Research_Tools.pdf
- Bagheri, S.H.R., Asghari, A.M., Farhadi, M., Shamshiri, A.R., Kabir, A., Kamrava, S.K., Jalessi, M., Mohebbi, A., Alizadeh, R., Honarmand, A.A., et al. 2020. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak. *medRxiv*, 2020.03.23.20041889. <https://doi.org/10.1101/2020.03.23.20041889>
- Baig, A.M., Khaleeq, A., Ali, U., and Syeda, H. 2020. Evidence of the covid-19 virus targeting the cns: Tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS Chemical Neuroscience*.
- Bartoshuk, L. M., Duffy, V. B., Fast, K., Green, B. G., Prutkin, J., & Snyder, D. J. (2003). Labeled scales (eg, category, Likert, VAS) and invalid across-group comparisons: what we have learned from genetic variation in taste. *Food Quality and Preference*, 14(2), 125-138.
- Beltrán-Corbellini, Á., Chico-García, J.L., Martínez-Poles, J., Rodríguez-Jorge, F., Natera-Villalba, E., Gómez-Corral, J., Gómez-López, A., Monreal, E., Parra-Díaz, P., Cortés-Cuevas, J.L., et al. 2020. Acute-onset smell and taste disorders in the context of covid-19: A pilot multicenter pcr-based case-control study. *European Journal of Neurology*.
- Bonfils, P., Avan, P., Faulcon, P., and Malinvaud, D. 2005. Distorted odorant perception: Analysis of a series of 56 patients with parosmia. *Archives of Otolaryngology - Head and Neck Surgery*. 131:107–112. <https://doi.org/10.1001/archotol.131.2.107>
- Brann, D.H., Tsukahara, T., Weinreb, C., Logan, D.W., and Datta, S.R. 2020. Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients. *bioRxiv*. 2020.03.25.009084. <https://doi.org/10.1101/2020.03.25.009084>
- Charrad, M., Ghazzali, N., Boiteau, V., and Niknafs, A. 2014. NbClust: An rpackage for determining the relevant number of clusters in a data set. *Journal of Statistical Software*. 61:1–36. Retrieved from <http://www.jstatsoft.org/v61/i06/>

Chen, R., Wang, K., Yu, J., Chen, Z., Wen, C., and Xu, Z. 2020. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. *bioRxiv*. 2020.04.07.030650. <https://doi.org/10.1101/2020.04.07.030650>

Dalton, P., and Hummel, T. 2000. Chemosensory function and response in idiopathic environmental intolerance. *Occupational Medicine*. 15:539–556.

Doty, R.L. 2001. Olfaction. *Annual Review of Psychology*. 52:423–452. <https://doi.org/10.1146/annurev.psych.52.1.423>

Duffy, V.B., and Hayes, J.E. 2019. Biological Basis and Functional Assessment of Oral Sensation. In: H.L. Meiselman, ed. *Handbook of Eating and Drinking: Interdisciplinary Perspectives*. Cham: Springer International Publishing. pp. 1–25. https://doi.org/10.1007/978-3-319-75388-1_22-1

Fark, T., and Hummel, T. 2013. Olfactory disorders: Distribution according to age and gender in 3,400 patients. *European Archives of Oto-Rhino-Laryngology*. 270:777–779. <https://doi.org/10.1007/s00405-012-2108-2>

Fodoulou, L., Tuberosa, J., Rossier, D., Landis, B.N., Carleton, A., and Rodriguez, I. (2020). SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium. *bioRxiv*, 2020.2003.2031.013268.

Frasnelli, J., Landis, B., Heilmann, S., Hauswald, B., Hüttenbrink, K., Lacroix, J., Leopold, D., and Hummel, T. 2004. Clinical presentation of qualitative olfactory dysfunction. *European Archives of Oto-Rhino-Laryngology and Head & Neck*. 261:411–415.

Gane, S.B., Kelly, C., and Hopkins, C. 2020. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology*. <https://doi.org/10.4193/Rhin20.114>

Giacomelli, A., Pezzati, L., Conti, F., Bernacchia, D., Siano, M., Oreni, L., Rusconi, S., Gervasoni, C., Ridolfo, A.L., Rizzardini, G., et al. 2020. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. <https://doi.org/10.1093/cid/ciaa330>

Gibson, J.J. 1966. *The senses considered as perceptual systems*. Houghton Mifflin, Boston, MA.

Green, B.G. 1996. Chemesthesis: Pungency as a component of flavor. *Trends in Food Science & Technology*. 7:415–420.

Green, B.G. 2012. Chemesthesis and the chemical senses as components of a "chemofensor complex". *Chemical Senses*. 37:201–206.
<https://doi.org/10.1093/chemse/bjr119>

Gudziol, H., & Hummel, T. (2007). Normative values for the assessment of gustatory function using liquid tastants. *Acta oto-laryngologica*, 127(6), 658-661.

Haldrup, M., Johansen, M.I., and Fjaeldstad, A.W. 2020. Lugte- og smagstab som primære symptom på COVID-19. *Ugeskr Læger*. 3–5.

Haro-Licer, J. de, Roura-Moreno, J., Vizitiu, A., González-Fernández, A., and González-Ares, J.A. 2013. Long term serious olfactory loss in colds and/or flu. *Acta Otorrinolaringologica (English Edition)*. 64:331–338.

Hayes, J.E. 2019. Influence of Sensation and Liking on Eating and Drinking. In: H.L. Meiselman, ed. *Handbook of Eating and Drinking: Interdisciplinary Perspectives*. Cham: Springer International Publishing. pp. 1–25. https://doi.org/10.1007/978-3-319-75388-1_21-1

Henkin, R. I., & Shallenberger, R. S. (1970). Aglycogeusia: the inability to recognize sweetness and its possible molecular basis. *Nature*, 227(5261), 965-966.

Hoffman, H.J., Rawal, S., Li, C.-M., and Duffy, V.B. 2016. New chemosensory component in the us national health and nutrition examination survey (nhanes): First-year results for measured olfactory dysfunction. *Reviews in Endocrine and Metabolic Disorders*. 17:221–240.

Holbrook, E.H., Leopold, D.A., and Schwob, J.E. 2005. Abnormalities of axon growth in human olfactory mucosa. *The Laryngoscope*. 115:2144–2154.

Hopkins, C., Surda, P., and Kumar, N. 2020. Presentation of new onset anosmia during the COVID-19 pandemic. *Rhinology*. <https://doi.org/10.4193/Rhin20.116>

Hummel, T., Landis, B.N., and Hüttenbrink, K.-B. 2011. Smell and taste disorders. *GMS Curr Top Otorhinolaryngol Head Neck Surg*. 10. <https://doi.org/10.3205/cto000077>

Huque, T., Cowart, B. J., Dankulich-Nagrudny, L., Pribitkin, E. A., Bayley, D. L., Spielman, A. I., ... & Brand, J. G. (2009). Sour ageusia in two individuals implicates ion channels of the ASIC and PKD families in human sour taste perception at the anterior tongue. *PLoS One*, 4(10).

Hwang, C.S. 2006. Olfactory neuropathy in severe acute respiratory syndrome: Report of a case. *Acta Neurologica Taiwanica*. 15:26–28.

Iannilli, E., Leopold, D.A., Hornung, D.E., and Hummel, T. 2019. Advances in Understanding Parosmia: An fMRI Study. *Orl*. 81:185–192.
<https://doi.org/10.1159/000500558>

Iravani, B., Arshamian, A., Ravia, A., Mishor, E., Snitz, K., Shushan, S., Roth, Y., Perl, O., Honigstein, D., Weissgross, R., Karagach, S., Ernst, G., Okamoto, M., Mainen, Z., Monteleone, E., Dinnella, C., Spinelli, S., Marino-Sanchez, F., Ferdenzi, C., Smeets, M., Touhara, K., Bensafi, M., Hummel, H., Sobel, N., Lundström, J.N. *Chemical Senses*, , bjaa034, <https://doi.org/10.1093/chemse/bjaa034>

Jeffreys, H. 1961. *Theory of probability*, Clarendon. Oxford.

Kalva, J.J., Sims, C.A., Puentes, L.A., Snyder, D.J., and Bartoshuk, L.M. 2014. Comparison of the hedonic general labeled magnitude scale with the hedonic 9-point scale. *Journal of Food Science*. 79:S238—S245.

Landis, B.N., Hummel, T., Hugentobler, M., Giger, R., and Lacroix, J. 2003. Ratings of overall olfactory function. *Chemical Senses*. 28:691–694.

Lechien, J.R., Cabaraux, P., Chiesa-Estomba, C.M., and Khalife, M. 2020a. Objective olfactory testing in patients presenting with sudden onset olfactory dysfunction as the first manifestation of confirmed covid-19 infection. Retrieved from Medrxiv.org.
<https://doi.org/10.1101/2020.04.15.20066472>

Lechien, J.R., Chiesa-Estomba, C.M., De Siati, D.R., Horoi, M., Le Bon, S.D., Rodriguez, A., Dequanter, D., Blecic, S., El Afia, F., Distinguin, L., et al. 2020b. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study.
<https://doi.org/10.1007/s00405-020-05965-1>

Lee, M.D., and Wagenmakers, E.-J. 2013. New York, NY: Cambridge University Press.

Lê, S., Josse, J., and Husson, F. 2008. FactoMineR: An r package for multivariate analysis. *Journal of Statistical Software*. 25:1–18.

Lötsch, J., and Hummel, T. 2006. The clinical significance of electrophysiological measures of olfactory function. *Behavioural Brain Research*. 170:78–83.
<https://doi.org/10.1016/j.bbr.2006.02.013>

Lötsch, J., & Hummel, T. (2019). Clinical usefulness of self-rated olfactory performance—a data science-based assessment of 6000 patients. *Chemical senses*, 44(6), 357-364.

Lugaz, O., Pillias, A. M., & Faurion, A. (2002). A new specific ageusia: some humans cannot taste L-glutamate. *Chemical senses*, 27(2), 105-115.

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., et al. 2020. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurology*.
<https://doi.org/10.1001/jamaneurol.2020.1127>

Marwick, B. 2019. rrttools: Creates a reproducible research compendium (R package version 0.1. 0)[Computer software manual]. <https://github.com/benmarwick/rrttools>

McDonald, S.T., Bolliet, D.A., and Hayes, J.E. 2016. Chemesthesis: Chemical Touch in Food and Eating. John Wiley & Sons. <https://doi.org/10.1002/9781118951620>

Menni, C., Valdes, A., Freydin, M.B., Ganesh, S., Moustafa, J.E.-S., Visconti, A., Hysi, P., Bowyer, R.C.E., Mangino, M., Falchi, M., et al. 2020. Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. medRxiv. 2020.04.05.20048421. <https://doi.org/10.1101/2020.04.05.20048421>

Moein, S.T., Hashemian, S.M., Mansourafshar, B., Khorram-Tousi, A., Tabarsi, P., and Doty, R.L. 2020. Smell dysfunction: A biomarker for covid-19. In: *International Forum of Allergy & Rhinology*. Wiley Online Library. <https://doi.org/10.1002/alr.22587>

Morey, R.D., and Rouder, J.N. 2018. BayesFactor: Computation of Bayes Factors for Common Designs. <https://cran.r-project.org/package=BayesFactor>

Moshontz, H., Campbell, L., Ebersole, C.R., IJzerman, H., Urry, H.L., Forscher, P.S., Grahe, J.E., McCarthy, R.J., Musser, E.D., Antfolk, J., et al. 2018. The Psychological

Science Accelerator: Advancing psychology through a distributed collaborative network. *Advances in Methods and Practices in Psychological Science*. 1:501–515.

Nordin, S., and Brämerson, A. 2008. Complaints of olfactory disorders: Epidemiology, assessment and clinical implications. *Current Opinion in Allergy and Clinical Immunology*. 8:10–15. <https://doi.org/10.1097/ACI.0b013e3282f3f473>

Oleszkiewicz, A., Kunkel, F., Larsson, M., and Hummel, T. 2020. Consequences of undetected olfactory loss for human chemosensory communication and well-being. *Philosophical Transactions of the Royal Society B*. 375:20190265.

Patel, Z.M. 2020. Correspondence: Reflections and new developments within the COVID-19 pandemic. *International Forum of Allergy & Rhinology*. alr.22582. <https://doi.org/10.1002/alr.22582>

Patil, I., and Powell, C. 2018. Ggstatsplot: “Ggplot2” based plots with statistical details. CRAN. Retrieved from <https://cran.r-project.org/web/packages/ggstatsplot>

Pellegrino, R., Cooper, K. W., Di Pizio, A., Joseph, P. V., Bhutani, S., & Parma, V. 2020. Corona viruses and the chemical senses: Past, present, and future. *Chemical Senses*, bjaa031, <https://doi.org/10.1093/chemse/bjaa031>

Pellegrino, R., Walliczek-Dworschak, U., Winter, G., Hull, D., and Hummel, T. 2017. Investigation of chemosensitivity during and after an acute cold. In: *International Forum of Allergy & Rhinology*. Wiley Online Library. pp. 185–191.

Pilkova, L., Novakova, M., & Pokorný, J. (1991). Naming and identification of tastes in aqueous solutions. *Food/Nahrung*, 35(9), 999-1002.

Rawal, S., Hoffman, H. J., Honda, M., Huedo-Medina, T. B., & Duffy, V. B. (2015). The taste and smell protocol in the 2011–2014 US National Health and Nutrition Examination Survey (NHANES): test–retest reliability and validity testing. *Chemosensory perception*, 8(3), 138-148.

Reden, J., Maroldt, H., Fritz, A., Zahnert, T., and Hummel, T. 2007. A study on the prognostic significance of qualitative olfactory dysfunction. *European Archives of Oto-Rhino-Laryngology*. 264:139–144. <https://doi.org/10.1007/s00405-006-0157-0>

Ren, Y., Yang, L., Guo, Y., Xutao, M., Li, K., and Wei, Y. 2012. Intranasal trigeminal chemosensitivity in patients with postviral and post-traumatic olfactory dysfunction. *Acta Oto-Laryngologica*. 132:974–980.

Rombaux, P., Martinage, S., Huart, C., and Collet, S. 2009. Post-infectious olfactory loss: A cohort study and update. *Acta Oto-Rhino-Laryngologica Belgica*. 8:89.

Rozin, P. 1982. “Taste-smell confusions” and the duality of the olfactory sense. *Perception & Psychophysics*. 31:397–401. <https://doi.org/10.3758/BF03202667>

Rubin, D.I., and Daube, J.R. 1999. Subacute sensory neuropathy associated with Epstein-Barr virus. *Muscle and Nerve*. 22:1607–1610.

Schönbrodt, F.D., and Wagenmakers, E.-J. 2018. Bayes factor design analysis: Planning for compelling evidence. *Psychonomic Bulletin & Review*. 25:128–142.

Schönbrodt, F.D., Wagenmakers, E.-J., Zehetleitner, M., and Perugini, M. 2017. Sequential hypothesis testing with Bayes factors: Efficiently testing mean differences. *Psychological Methods*. 22:322.

Shepherd, G.M. 2006. Smell images and the flavour system in the human brain. *Nature*. 444:316–321. <https://doi.org/10.1038/nature05405>

Soler, Z.M., Patel, Z.M., Turner, J.H., and Holbrook, E.H. 2020. A primer on viral-associated olfactory loss in the era of COVID-19. In: *International Forum of Allergy & Rhinology*. Wiley Online Library.

Spence, C., Auvray, M., and Smith, B. 2014. Confusing Tastes with Flavours. *Perception and Its Modalities*. 247–274.

Sungnak, W., Huang, N., Bécavin, C., Berg, M., Queen, R., Litvinukova, M., Talavera-López, C., Maatz, H., Reichart, D., Sampaziotis, F., et al. 2020. SARS-cov-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nature Medicine*. 1–7.

Team R Core Development. 2013. R: a language and environment for statistical computing. Retrieved from <http://www.r-project.org/>

Varga, Z., Flammer, A.J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A.S., Mehra, M.R., Schuepbach, R.A., Ruschitzka, F., and Moch, H. 2020. Endothelial cell infection and endotheliitis in covid-19. *The Lancet*.

Veldhuizen, M., Parma, V., Reed, D., Liuzza, M.T. 2020. GCCR001 - Quantifying smell, taste and chemesthesis changes in covid19: A multi-national study. OSF. Retrieved from osf.io/auhs8.

Venkatakrisnan, A., Puranik, A., Anand, A., Zemmour, D., Yao, X., Wu, X., Chilaka, R., Murakowski, D.K., Standish, K., Raghunathan, B., et al. 2020. Knowledge synthesis from 100 million biomedical documents augments the deep expression profiling of coronavirus receptors. *arXiv Preprint arXiv:200312773*.

Vetter, P., Vu, D.L., L'Huillier, A.G., Schibler, M., Kaiser, L., and Jacquerioz, F. 2020. Clinical features of covid-19. *Bmj*. m1470. <https://doi.org/10.1136/bmj.m1470>

Welge-Lüssen, A., Hummel, T., Stojan, T., and Wolfensberger, M. 2005. What is the correlation between ratings and measures of olfactory function in patients with olfactory loss? *American Journal of Rhinology*. 19:567–571. <https://doi.org/10.1177/194589240501900606>

Welge-Lüssen, A., Dörig, P., Wolfensberger, M., Krone, F., & Hummel, T. (2011). A study about the frequency of taste disorders. *Journal of neurology*, 258(3), 386-392.

Workman, A.D., Welling, D.B., Carter, B.S., Curry, W.T., Holbrook, E.H., Gray, S.T., Scangas, G.A., and Bleier, B.S. 2020. Endonasal instrumentation and aerosolization risk in the era of COVID-19: simulation, literature review, and proposed mitigation strategies. *International Forum of Allergy & Rhinology*.

World Health Organization. 2020. Q&A on coronaviruses (COVID-19). Retrieved on May 1, 2020 from <https://www.who.int/news-room/q-a-detail/q-a-coronaviruses>

Yan, C.H., Faraji, F., Prajapati, D.P., Boone, C.E., and DeConde, A.S. 2020a. Association of chemosensory dysfunction and covid-19 in patients presenting with influenza-like symptoms. In: *International Forum of Allergy & Rhinology*. Wiley Online Library.

Yan, C.H., Faraji, F., Prajapati, D.P., Ostrander, B.T., and DeConde, A.S. 2020b. Self-reported olfactory loss associates with outpatient clinical course in Covid-19. *International Forum of Allergy & Rhinology*. <https://doi.org/10.1002/alr.22592>

Yu, H. 2017. Bootcluster: Bootstrapping estimates of clustering stability. CRAN. Retrieved from <https://cran.r-project.org/package=bootcluster>.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., et al. 2020. A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*. 382:727–733. <https://doi.org/10.1056/NEJMoa2001017>

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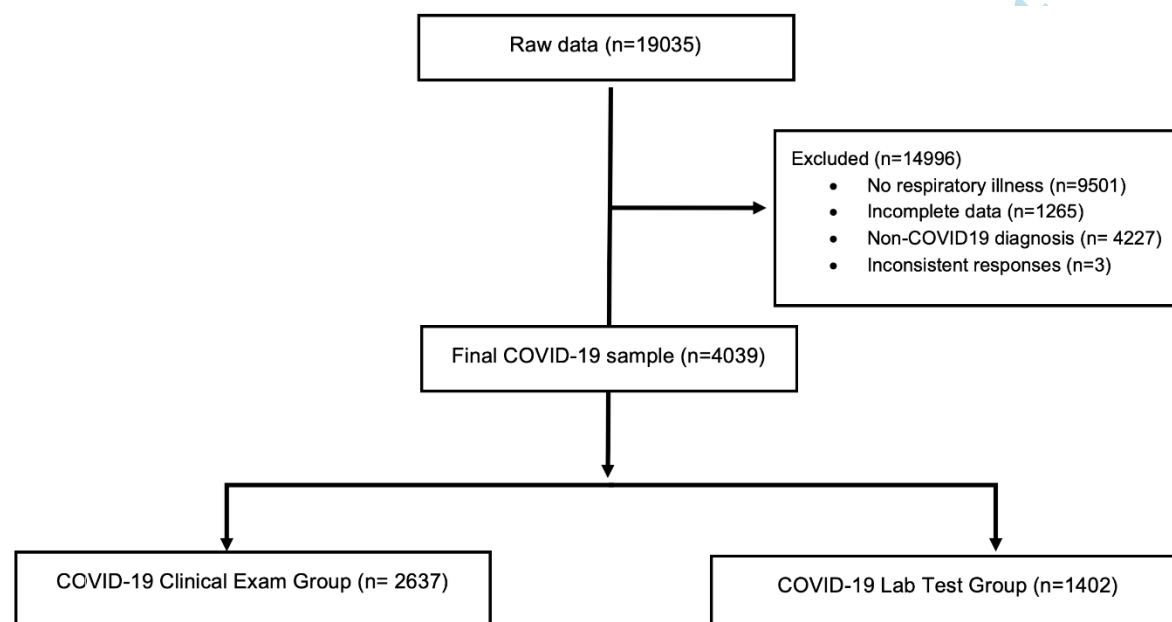
Figure 1

Figure 2

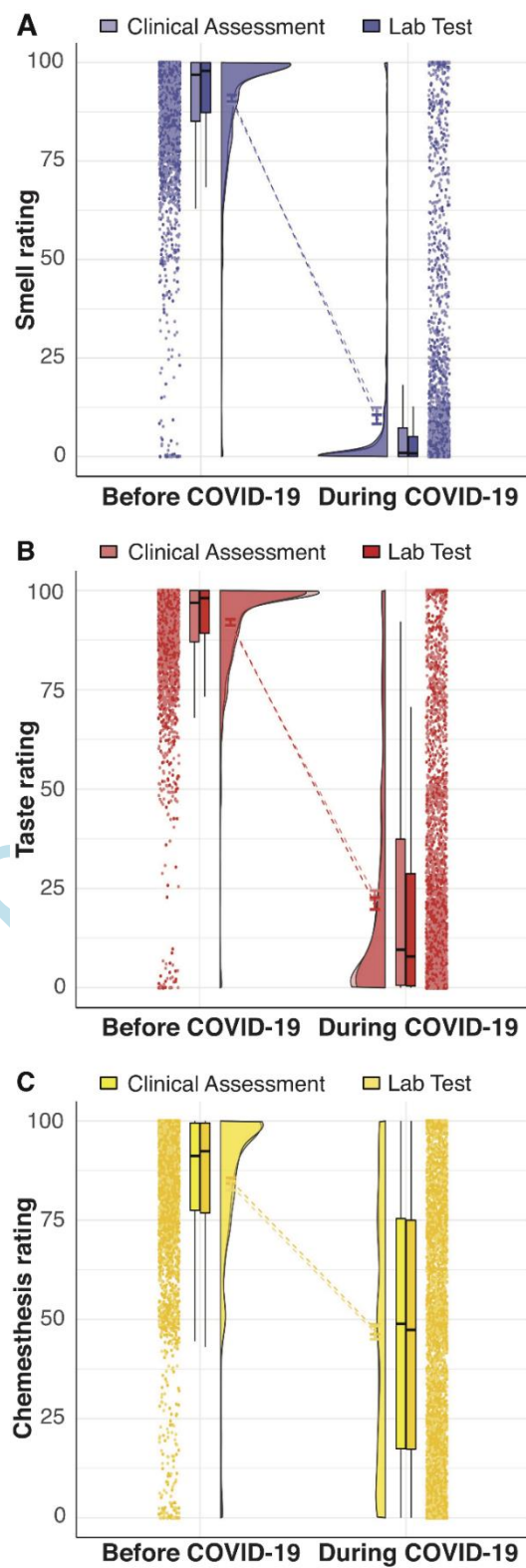


Figure 3

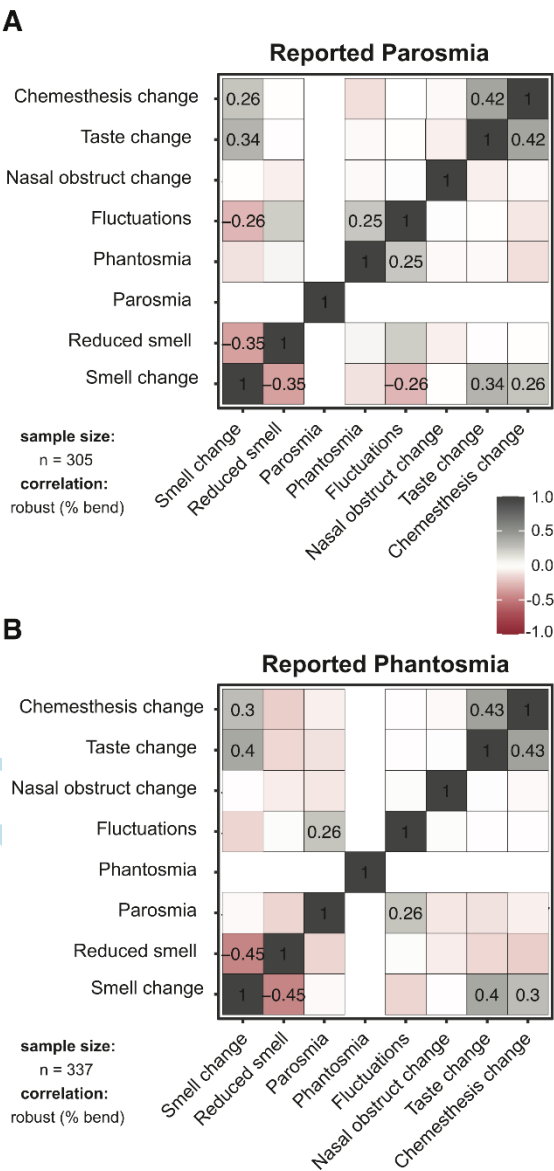


Figure 4

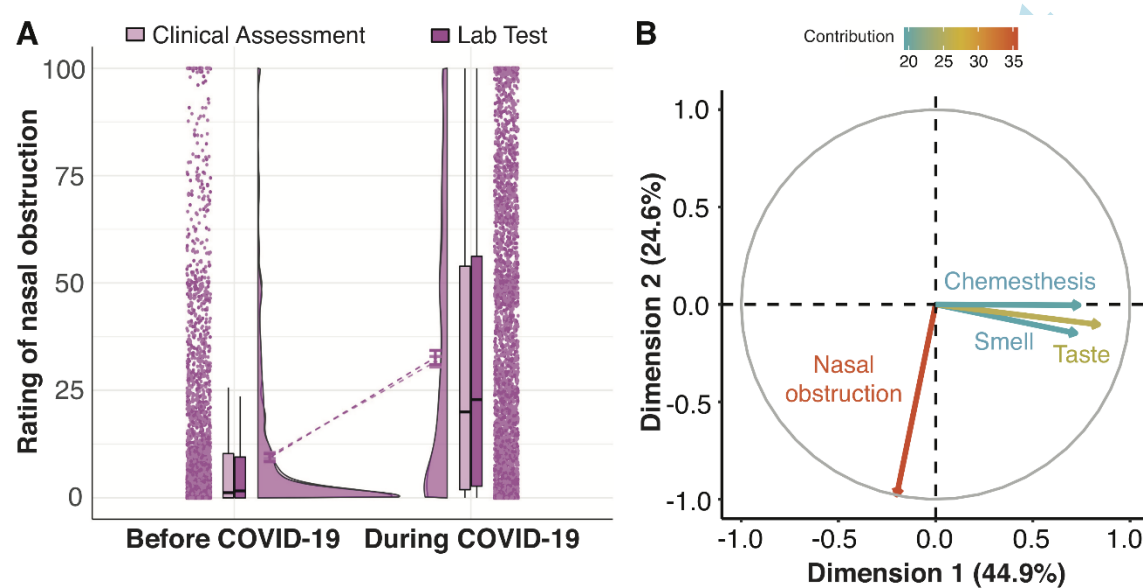


Figure 5

